Bożena Ziółkowska-Graca[1], Aleksander Kania[1], Grażyna Zwolińska[2], Ewa Niżankowska-Mogilnicka[1]

[1]Division of Pulmonary Diseases, Department of Internal Medicine, Jagiellonian University School of Medicine, Krakow, Poland
Head of unit: Prof. Ewa Niżankowska-Mogilnicka
[2]Department of Neurology, Jagiellonian University College of Medicine, Krakow, Poland
Head of unit: Prof. Andrzej Szczudlik

Adult form of Pompe disease

Abstract

Pompe disease (glycogen-storage disease type II) is an autosomal recessive disorder caused by a deficiency of lysosomal acid α-glucosidase (GAA), leading to the accumulation of glycogen in the lysosomes primarily in muscle cells. In the adult form of the disease, proximal muscle weakness is noted and muscle volume is decreased. The infantile form is usually fatal. In the adult form of the disease the prognosis is relatively good. Muscle weakness may, however, interfere with normal daily activities, and respiratory insufficiency may be associated with obstructive sleep apnea. Death usually results from respiratory failure. Effective specific treatment is not available. Enzyme replacement therapy with recombinant human GAA (rh-GAA) still remains a research area.

We report the case of a 24-year-old student admitted to the Department of Pulmonary Diseases because of severe respiratory insufficiency. Clinical symptoms such as dyspnea, muscular weakness and increased daytime sleepiness had been progressing for 2 years. Clinical examination and increased blood levels of CK suggested muscle pathology. Histopathological analysis of muscle biopsy, performed under electron microscope, confirmed the presence of vacuoles containing glycogen. Specific enzymatic activity of α-glucosidase was analyzed confirming Pompe disease.

The only effective method to treat respiratory insufficiency was bi-level positive pressure ventilation. Respiratory rehabilitation was instituted and is still being continued by the patient at home. A high-protein, low-sugar diet was proposed for the patient. Because of poliglobulia, low molecular weight heparin was prescribed. The patient is eligible for experimental replacement therapy with rh-GAA.

Key words: Pompe disease

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Case study

A 24-year-old student was admitted to the Department of Pulmonary Disease from the Department of Neurological Disease. His condition was described as very serious because of rest dyspnea, considerable muscular weakness, increased daytime sleepiness and significant bradyphrenia.

The physical examination confirmed considerable rest dyspnea which was slightly decreased in a sitting position, fatigue when attempting to speak at length, sleepiness and bradyphrenia.

Cyanosis of the lips and mucosae, lacrimation and congestion of the eyes, and substantial peripheral oedema were observed. He had an enlarged liver, heart rate increased to 100/min and increased second heart sound above the pulmonary valve. The patient had had limited motor skills since childhood. At the age of 10 a routine check-up revealed increased values of both liver enzymes and creatine kinase in his blood. Subsequent tests excluded viral hepatitis but no further diagnostics were conducted. The patient was under periodic observation. From the age of 22 a substantial dete-

Address for correspondence: Aleksander Kania, Division of Pulmonary Diseases, Dept. of Internal Medicine, Jagiellonian University School of Medicine, 8 Skawińska Str., 31–066 Kraków, ph.: (012) 430 52 66; fax: (012) 430 52 03, e-mail: ollekk@interia.pl

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rioration of the patient's health had been observed. Muscular weakness of the lower, and later the upper, limbs was noted. At that time peripheral oedema of lower limbs and cyanosis of the lips and mucosae also appeared. After a few months the patient's condition further deteriorated. He complained of fatigue, daytime sleepiness, problems with concentration, and bradyphrenia. Peripheral oedema aggravated, his abdominal circumference increased, and central cyanosis, lacrimation and serious conjunctival reddening were observed.

During hospitalization, laboratory tests revealed poliglobulia: Hb 17.8 g/dl, HCT 57.2%, RBC 7.5 mln/μl, and abnormal values of enzymes: AspAT 240 U/l, ALAT 260 U/l, CK 2680 U/l, CK-MB 71 U/l. Gasometric examination of arterial blood showed total respiratory failure: pH 7.25, pO_2 47 mm Hg, and pCO_2 70 mm Hg. No abnormalities were found in thorax X-ray or high resolution computer tomography. EKG examination showed sinus rhythm 100/min, normal electrical axis, negative T waves in leads III and aVL and deep S waves in leads V1–V3. Echocardiography revealed increased right ventricle of the heart with average pressure in pulmonary artery app. 70 mm Hg, paradoxical ventricular septal movement and widened trunk of the pulmonary artery (3.74 cm).

Pathology of the respiratory and circulatory systems was eliminated as the source of respiratory failure, and myogenic background was suspected. Histological examination of a deltoid muscle biopsy showed the presence of vacuoles, suggesting the accumulation of glycogen, which is typical of Pompe disease. The diagnosis was fully confirmed upon determination of the ratio of specific lysosomal α-glucosidase of leukocytes in a dry drop of blood with pH 3.8 with and without the presence of the inhibitor. This activity was profoundly decreased (0.08, with control values ranging from 0.29 to 0.49). Moreover, the ratio of enzymatic activity with pH 4.5–6.0 was only 0.01, while for a healthy individual it exceeds 0.37. This result further confirmed the diagnosis of Pompe disease. The activity of lysosomal α-glucosidase of leukocytes was analyzed in the Metabolic Laboratory in the Department of Genetics of the Institute of Psychiatry and Neurology.

Treatment

Due to the patient's respiratory failure, bi-level positive pressure ventilation was used in his treatment. The algorithm S (spontaneous) and a pressure of 12 mbar for IPAP (inspiratory positive airway pressure) and 6 mbar for EPAP (expiratory positive airway pressure) proved sufficient to normalize gasometric parameters (pO_2 60 mm Hg, pCO_2 48 mm Hg, pH 7.39). Intensive respiratory rehabilitation was instituted and is still being continued by the patient at home. A low-sugar, high-protein diet was recommended as standard procedure. Because of poliglobulia, low molecular weight heparin was prescribed. The patient's condition improved gradually; respiratory insufficiency receded completely and the parameters were normal. Subsequent laboratory tests after 2 months showed normalization of blood cell count and decreased CK level to 1271 U/l. Echocardiography control test did not indicate raised pressure in the pulmonary artery. Daytime sleepiness receded. The patient felt fine; he was able to make more and more effort and continued his studies. He reported a considerable improvement in the quality of life. He became a member of an international support group for people suffering from Pompe disease and was qualified for experimental therapy with recombined enzyme of α-glucosidase rhGAA (drug: Myozyme).

Discussion

Pompe disease (type II glycogenosis; GSD II) is a glycogen storage disease. It is a rare genetic autosomal recessive disorder. It is a deficiency of lysosomal acid α-1.4-glucosidase (acid maltase) — the enzyme responsible for eliminating excess glycogen in lysosomal vacuoles of cells. The result is the accumulation of glycogen in the body, especially in liver cells, skeletal muscles, the heart, glia cells, nucleus of the brain trunk and anterior horn of the spinal cord. This is the only glycogenosis in which glycogen is accumulated in cell lysosomes and not cytoplasm.

The disorder is very rare. It was first described in 1932 by a Dutch pathologist J.C. Pompe. It is unknown precisely how many people suffer from it. It occurs in approximately 1 out of 40 000 births. Less than 200 000 people in the United States and no more than 5000–10 000 in Europe are affected. Although it occurs in people of all races, it affects African Americans more often (1/14 000 births) than Caucasians (1/60 000 adults and 1/100 000 children).

Clinical picture

The disease has many phenotypes. Myopathy occurs in each phenotype, but they differ with regard to the age when symptoms appear, the degree to which organs are affected by the pathogenic process, and how serious the clinical symptoms

are. The most severe form of the disease is infantile form, which is manifested by decreased muscle tone, tongue hypertrophy, hepatomegaly, and congestive heart failure caused by hypertrophic cardiomyopathy. Death usually occurs before the second birthday as a consequence of cardiorespiratory failure or aspiration pneumonia. The activity of α-glucosidase enzyme in these patients is less than 1% of the norm.

The juvenile form is mainly characterized by slowly progressing symptoms in skeletal muscles. Typical symptoms include: retarded stages of motor development, limited ability to walk, difficulty in swallowing, weakness of proximal muscles in the extremities and respiratory insufficiency due to respiratory muscles being affected by pathogenic processes. Death usually occurs before the patient is 20 years old. The activity of α-glucosidase enzyme in these patients is less than 10% of the norm.

The adult form of Pompe disease is manifested by slowly progressing proximal muscle weakness including respiratory muscles. The upper limb girdle muscles, prevertebral muscles and diaphragm are affected the most. The primary symptom may be respiratory insufficiency, and as a result: sleepiness, morning headaches, proper respiration only in standing position, effort dyspnea, and symptoms of obstructive sleep apnea. Other noted symptoms include enlarged liver and, less often, tongue hypertrophy which interferes with swallowing and mastication of food.

Laboratory tests show raised concentrations of creatine kinase, aspartate transaminase and lactate dehydrogenase in serum. In electromyographic investigation, features of myopathy with hyperexcitability of muscle fibres and pseudotonic impulses are often visible. The activity of α-glucosidase enzyme in these patients is less than 40% of the norm.

A lack of activity of α-glucosidase enzyme or its lower level in a biopsy sample from the affected area allows diagnosis of the disorder. Most often a sample of skin or muscle is collected. Additionally, the presence of vacuoles which positively stain towards glycogen in bioptate cells is noted.

Treatment

Until recently no effective method to treat Pompe disease existed. At present, enzymatic replacement is the most important therapy. The research on this method, although it has been conducted for some time, has entered an advanced stage recently. Attempts to acquire recombined α-glucosidase isolated from transgenic rabbit's milk have been successful. The alternative for this method is to acquire the enzyme from Chinese hamster ovary cells after prior introduction of α-glucosidase.

The therapeutic action of this substance is based on the assumption that the enzyme, having been administered intravenously, is intercepted by the cells of skeletal muscles and the heart through a receptor mechanism linked with mannose-6-phosphorate receptor. In this way the concentration of the enzyme within the cells should increase.

In recent years numerous clinical tests have been conducted which aim at assessing the effectiveness of the enzyme. The tests have mainly been carried out on neonates and infants up to the age of 6 months suffering from Pompe disease. The infantile form of the disease is considerably more frequent and more severe than that found in older children and adults. After a few months of treatment a substantial improvement in the children's clinical state was noted. The observations that were made included improvement of physical strength, which was assessed based on the children's physical development, as well as a significant change in the microscope picture of the examined muscle tissue (less intensive staining by PAS method towards the presence of glycogen). Cardiological changes have also been monitored by heart echography examinations. A decrease in left-ventricular mass index to a value which approximates the norm has been observed in all treated children, although the initial value exceeded the standard almost by a factor of three.

In medical references only one study is available discussing the results of research done on adult patients. Three patients aged 11, 16 and 32 were administered the enzyme intravenously in weekly doses of 10–20 mg/kg. Significantly improved muscular strength and increased respiratory efficiency parameters were observed in all 3 patients. With larger doses it was possible to achieve a sizable increase of the enzyme activity in muscles. The best results were noted in the youngest patient, who was least affected by the disease. The indications of progress in the other 2 patients were primarily disability reduction and cardiorespiratory stabilization. It was observed that the improvement was greater in groups of muscles that were used more often. The administered preparation usually caused no side effects that would require further treatment.

In 2006 the Federal Drug Administration approved the clinical use of α-glucosidase under the trade name Myozyme, as the first and only drug to be used in Pompe disease replacement therapy.

For treating milder forms of the disorder, which occur in youths and adults, following a low-sugar, high-protein diet is quite significant. Physical rehabilitation is vital in the treatment of all

types of the disease. If respiratory failure or sleep apnea occur, it is necessary to apply non-invasive mechanical ventilation with continuous positive pressure in the respiratory tract, preferably by bi-level method.

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